Early risk stratification in patients with chest pain
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Chapter 2

Diagnostic procedures in rule-out protocols:
background and rationale

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Submitted
INTRODUCTION

Ruling out acute coronary syndrome (ACS) in patients presenting with acute chest pain at the emergency room can be a challenge. These patients are a heterogeneous group who have widely varying risks: 8% have acute myocardial infarction (AMI), 15% are classified as having unstable angina (UA), and more than 50% of patients hospitalized for ACS are found not to have AMI or unstable angina at discharge(28). On the other hand, 2.1% of patients presenting with acute chest pain at the emergency department are discharged home with undetected AMI and 2.3% with missed diagnosis of unstable angina(3). The mortality in patients discharged home with missed AMI is four times greater than in those who are admitted to the hospital(4). Therefore, accurate yet simple non-expensive methods for risk assessment, which may lead to rapid triage and management of chest pain patients, are important.

Several rule-out protocols have been designed to better risk stratify patients in the emergency department setting. The aim of these rule-out protocols is to identify the patients who can be discharged home safely with an acceptable low risk of future cardiac events. The recommended strategy is the combination of an observation period, serial electrocardiogram (ECG) and serial biochemical marker measurements, followed by a stress test, either pre-discharge or within 72 hours at the outpatient clinic(5;18). However, this recommendation, based on the guidelines for the management patients with unstable angina and patients with non-ST-segment elevation myocardial infarction, has the level of evidence of C (i.e. lowest rank, expert consensus is the primary basis for the recommendation). In patients with unstable angina or AMI, who are at high risk, the specificity of a test is more relevant whereas in patients with chest pain undergoing a rule-out protocol, who are at low to intermediate risk, high sensitivity is required.

In this article, we will discuss the different diagnostic tests that are used for risk stratification in rule-out protocols.
METHODS

Various diagnostic tools are used to evaluate the risk of patients with chest pain with low to intermediate risk who present to the emergency department. We will focus on clinical studies satisfying the following criteria: 1. prospective studies comprising more than 100 consecutive patients, 2. evaluation in the emergency department or chest pain unit, 3. low (to intermediate) risk chest pain patients, 4. follow-up after evaluation at the emergency department/after discharge.

For the definition of low risk patients, many studies refer to data from Goldman et al. (29) (30). Using clinical and electrocardiographic data, a predicted probability of myocardial infarction below (i.e. low risk) or above 7% (i.e. high risk) was identified (29). In low risk patients (less than 7% probability of myocardial infarction) without enzyme abnormalities and recurrent chest pain during 12 hours of observation the cardiac event rate was 0.9% (0.5% AMI and 0.4% cardiac death) 3-5 days after admission (31). In a more recent study, Goldman et al. identified four groups of patients categorized according to their risk of major cardiac events within 72 hours after admission: very low risk (<1%), low risk (approximately 4%), intermediate risk (approximately 8%) and high risk (>16%) (30). The categorization was based on the data (electrocardiogram (ECG), history of coronary artery disease and physical examination) available at the time of presentation to the emergency department. Other guidelines, such as the Agency for Health Care Policy and Research (AHCPR) guidelines (32), also categorize patients into low-, intermediate-, and high risk groups (i.e. short-term risk of fatal or non-fatal myocardial infarction) based on clinical and electrocardiographic data at presentation. These guidelines are used to decide where to admit patients (e.g. chest pain unit or coronary care unit).

In this article we will discuss studies evaluating different tests for risk stratification in low or intermediate risk patients (according to previous data, either data from Goldman et al. (29), AHCPR guidelines (32), or other) presenting with chest pain to the emergency department.
RESULTS

I. History and clinical features

The evaluation of acute chest pain should begin with a clinical history taking that focuses on the characteristics of pain, the time of onset, and the duration of symptoms and an examination that emphasizes vital signs and cardiovascular status (1).

It has been suggested that no single symptom is of overwhelming diagnostic importance of ACS, although combinations of symptoms identify high risk patients who should be admitted regardless of ECG findings (33). Goldman et al. described a protocol including clinical and electrocardiographic characteristics and compared this with the decision made by the physician: the protocol had a higher specificity (74 versus 71%) but similar sensitivity (88.0 vs. 87.8%) for myocardial infarction (29). In another study, they showed that it was possible to risk stratify patients presenting with chest pain in very low to high risk patients (0.6-16.1% risk of major complications in the 72 hours after presentation) using data available at presentation at the emergency room. The risk factors they identified were suspected AMI or ischemia on the ECG, systolic blood pressure below 110 mmHg, rales above the bases bilaterally, and exacerbation of known ischemic heart disease (30).

In a large prospective study comprising more than 10,000 patients presenting to the emergency department with symptoms suggestive of acute ischemia, chest pain (92% versus 71%, p=0.001) and nausea (30% versus 27%, p=0.003) as presenting symptoms and a past history of angina pectoris (63 versus 29%), AMI (45 versus 20%), or diabetes (31% versus 18%) were most often related with ACS (28). Another prospective study comprising 1743 patients with symptoms suggestive of acute ischemia, showed that classical risk factors did not predict the risk of acute ischemia in women, but in men the presence of diabetes and family history of AMI increased the risk significantly (p<0.05). However, the relative risks (2.4 and 2.1, respectively) were small compared to those conferred by chest pain (12.1) or by the ECG (abnormal ST segment (8.7), or an abnormal T wave (5.3))(34).

Patients with missed diagnosis of UA are more often women less than 55 years old (odds ratio for discharge, 6.7), patients with a normal or non-diagnostic ECG (odds ratio 3.3), patients with shortness of breath as their chief complaint (odds ratio 2.7), or non-white
patients (odds ratio 2.2). Patients with missed diagnosis of AMI have more often a normal or non-diagnostic ECG (odds ratio 7.7) or are non-white (odds ratio 4.5)(3). Although a typical history and clinical features may identify patients at high risk, its absence does not exclude patients at risk. Identification of ACS may be more difficult in young patients, women, non-white patients, patients with other presenting symptoms than chest pain, and in patients with a normal or non-diagnostic electrocardiogram. These patients in particular need further evaluation. However, even in patients with a typical history, further evaluation (electrocardiogram) may lead to early and accurate triage, such as the need of immediate intervention.

II. Admission Electrocardiogram

The ECG represents a safe, readily available, and inexpensive technology(33). It plays an essential role in guiding initial therapy and admission management of chest pain patients, especially in those with ECG changes indicative for ischemia, either transmural or non-transmural. In patients without such ECG changes, AMI may be present in 2-4% depending primarily on the presence of a history of coronary artery disease(1). A normal ECG, defined as not having Q waves, primary ST segment and T-wave changes, and non-diagnostic changes, is associated with a final diagnosis of non-ACS (51% versus 31% of the patients with acute coronary syndrome). On the other hand, a normal ECG at presentation is reported in 20% of patients with AMI and in 37% of patients with unstable angina (28). Thus, a normal (serial) ECG alone cannot be used to rule out ACS, even if obtained up to 12 hours after the onset of symptoms(35). Continuous 12 lead ST segment monitoring in combination with serial ECG’s cannot exclude ACS either (50.3% of patients with ACS showed no changes on serial ECG) (36). In addition, continuous 12 lead ST segment monitoring/serial ECG has only limited incremental diagnostic value compared to a standard rule out protocol, including serial CK-MB and initial ECG (the sensitivity for the diagnosis of ACS increased from 58% to 65% whereas the specificity decreased from 63% to 58%) if used in an intermediate risk (AHCPR) group(37).

Prognostic ECG changes have been described primarily in patients with an established diagnosis of ACS. However, recently, a prospective study showed that serial non-diagnostic ECG (defined as signs of left ventricular hypertrophy, bundle branch block, prior AMI, or the presence of non-specific ST-segment abnormalities) compared to
normal serial ECG was associated with future cardiac events (38;39) (table). Herren et al. showed that patients without ST segment changes during 6 hours of monitoring in combination with normal serial CK-MBmass were free from 30 days adverse cardiac events(40). Similar results were reported by Decker et al.(37), although they did not consider CK-MBmass results and their study group was smaller(37).

The standard 12-leads ECG has important limitations (such as, being a 10 second recording, imperfect sensitivity and specificity), however it may provide essential information when the diagnosis is not obvious by clinical symptoms alone. Therefore, a 12-lead ECG should be obtained as soon as possible in patients presenting with symptoms suggestive of myocardial ischemia, followed by serial ECG’s/continous ECG monitoring. ECG changes may identify high risk patients that need urgent treatment. However, a normal serial ECG/continous ECG monitoring alone cannot rule out ACS. As a consequence, in patients with chest pain, a non-typical history and a normal or non-diagnostic ECG, further testing is needed.

III. Biochemical markers

Several biochemical markers can be used in chest pain patients, e.g. markers of myocardial damage, markers of inflammation, markers of coagulation, and markers of left ventricular dysfunction. Markers of myocardial damage are a standard component of rule-out protocols. The other markers are under investigation.

a. Markers of myocardial damage

In the American College of Cardiology/American Heart Association guidelines for the management of patients with unstable angina and non-ST-elevation AMI it has been recommended that in patients with chest discomfort consistent with ACS, serial cardiac specific troponin is the preferred marker, but serial creatinine kinase-MBmass (CK-MBmass) is also acceptable(5;18). In patients presenting within 6 hours of presentation early markers of myocardial damage, such as CK-MB subforms, may be considered in addition to cardiac troponins(5;18;41).

Until recently, serial CK-MB was used as the diagnostic standard for AMI. It has been shown that the diagnosis of AMI can be made earlier with a higher sensitivity (up to 99%) if an increase between serial CK-MBmass values is considered as well(7;42;43).
For ruling out myocardial infarction myoglobin is an earlier marker (3-6 hours after the onset of symptoms) than CK-MB\textsubscript{mass} and troponin T but reaches a negative predictive value of only 89%. After 7 hours, CK-MB\textsubscript{mass} and troponin T have a higher negative predictive value than myoglobin(44).

Cardiac troponins are more specific for myocardial damage than CK-MB, rise several hours later than CK-MB\textsubscript{mass} and remain elevated for days depending on the size of the infarction. Recently, McCord et al. showed that the combination of normal troponin I and normal myoglobin values at admission and at 90 minutes may exclude AMI rapidly. The sensitivity (96.6%) and the negative predictive value (99.6%) did not improve if the combination of CK-MB and myoglobin was used or if extra blood sampling at 180 minutes was performed(45).

A study comparing troponin T and CK-MB in low risk chest pain patients (according to the algorithm by Goldman et al.(29)), showed that both tests had similar negative predictive values (87.2% and 86.3%, respectively) for future adverse events(11)(table). Higher negative predictive values for troponins (T and I) were found in a larger study comprising patients presenting with acute chest pain without ST segment elevation. The difference in negative predictive value may be explained by the different study population (<7% probability of AMI, including absence of new ST/T wave changes versus absence of ST elevation or documented AMI during the preceding two weeks), the follow-up (11 months versus 1 month), the definition of cardiac events, and the event rate(6)(table).

High negative predictive value for troponin T was also found in patients with a normal or non-diagnostic ECG, no-high risk clinical features and normal initial CK/CK-MB results(46)(table).

A negative cardiac troponin does not by itself exclude significant disease(47). Hillis et al. showed that 124/295 (42%) patients with low risk clinical and ECG features (≤7% risk of AMI) and negative serial troponin had objective evidence for significant coronary artery disease (i.e. a stress test showing ischemia or infarction and/or an angiogram showing significant coronary artery disease)(48). In addition, deFilippi et al. demonstrated that in 33/144 (23%) patients with negative serial troponin T, significant coronary artery disease was present (coronary angiography). Furthermore, it has been demonstrated that a substantial proportion of patients with negative serial troponin has major complications during short-term(8-10) and long-term(11) follow-up. Therefore, in patients with negative...
serial markers of myocardial necrosis, additional testing is needed to identify patients at risk for subsequent adverse cardiac events.

b. Markers of inflammation
The most widely studied (non-specific) marker of inflammation is C-reactive protein (CRP). Several studies have shown that CRP has prognostic value in addition to cardiac troponins. However, these studies comprised patients with unstable angina (12-15). So far, only one study showed that CRP (and erythrocyte sedimentation rate) may be used for further risk stratification in troponin negative chest pain patients presenting at the emergency department with normal or non-diagnostic ECG's (38) (table). Other studies are needed to confirm this finding.

Other markers of inflammation (e.g. myeloperoxidase, monocytes, soluble intercellular adhesion molecule-1, cytokines (Interleukin-6 and 8, Tumor Necrosis Factor-α)), marker of LV function (N-terminal pro-Brain Natriuretic Peptide), and markers of hemostasis (e.g. plasminogen activator inhibitor, p-selectin, fibrinogen) have not been evaluated in rule-out protocols yet. Recently, one study evaluated the baseline myeloperoxidase levels in unselected patients presenting with chest pain. In a subgroup consisting of 462 troponin T negative patients, the myeloperoxidase levels were significantly higher (median, 269 pM versus 158 pM) in patients who had major adverse cardiac events in the subsequent 30 days and 6 months (with increasing quartiles the odds ratios increased from 2 to 4) (49). This finding suggests that myeloperoxidase may have additional prognostic value in patients presenting with chest pain in whom myocardial necrosis is excluded by troponins. However, the clinical relevance of this marker (and other markers) in a rule-out setting should be investigated in future studies.

Negative serial troponins exclude myocardial necrosis but do not exclude significant coronary artery disease. Negative serial troponins in combination with low risk clinical and ECG features may identify patients at low risk for future cardiac events. However, even in such low risk patients, significant coronary artery disease may be present in more than 20% of the patients. In addition, patients with negative serial troponin may be at risk for major complications during follow-up. Other markers (such as, C-reactive protein, erythrocyte sedimentation rate or myeloperoxidase) may discriminate low and high risk patients within the group of patients with negative serial troponin. However, before using
these markers as part of rule out protocols they should be tested in larger prospective studies. Thus, at this moment only markers of myocardial damage, i.e. CK-MB<sub>mass</sub> or cardiac troponins, should be used for rule-out purposes.

IV. Evaluation of left ventricle function
Imaging modalities provide the ability to quantify the extent of jeopardized myocardium and localize ischemic territories. An echocardiogram or nuclear imaging test may be of value in chest pain patients for whom the initial history, physical examination, and ECG are not conclusive.

a. Resting echocardiogram
An echocardiogram may show new segmental wall motion abnormalities as a result of ischemia due to critical coronary artery disease. On the other hand, previous myocardial infarction can make it difficult to differentiate new from pre-existent wall motion abnormalities.
Regional wall motion abnormalities in the presence of normal wall thickness may indicate acute ischemia or evolving AMI. The severity of ischemia, its duration, and the extent of the ischemic zone may affect the persistence of wall motion abnormalities. Imaging performed after symptom resolution may be associated with reduced sensitivity. In addition, in patients with limited jeopardized myocardium, wall motion may be normal. Only a few prospective studies have been published regarding the usefulness of immediate echocardiography at the emergency room in the triage of chest pain patients(50-53). The sensitivity for the detection of AMI in these studies was high (85-100%). Echocardiography performed within 4 hours of presentation at the emergency room has additional prognostic value when added to baseline clinical variables and the ECG(51)(table). A normal echocardiogram was associated with an excellent negative predictive value (event rate of 0% (0/330)) during follow-up(53) (table).

b. Resting perfusion imaging
Myocardial perfusion imaging may be of value in chest pain patients with a normal or non-diagnostic ECG. Patients with prior AMI are likely to have resting myocardial perfusion defects and therefore will require subsequent repeat perfusion imaging to
differentiate new ischemia from old myocardial infarction. Thus, an initial rest perfusion image is of limited value in chest pain patients with prior myocardial infarction.

High sensitivities but low specificities for the diagnosis of AMI have been reported (53-58) (table). The specificity may increase significantly if patients with previous AMI are excluded from the analysis (71% to 80%, p=0.005)(55).

Several small studies have shown that a normal rest technetium-99M sestamibi imaging in chest pain patients with a normal or non-diagnostic ECG identifies low risk patients that can be discharged safely (rate of cardiac death, AMI or revascularization of 1.4-3% (59;60) and rate of AMI of 0.4%(54)).

Recently, a large randomized multicenter trial showed that immediate sestamibi perfusion imaging incorporated into a standard rule-out protocol (defined as the standard clinical evaluation strategy used in each hospital’s emergency department) (1215 patients) compared to the standard protocol alone (1260 patients) improved triage decision in patients with symptoms suggestive of acute ischemia, a normal or non-diagnostic ECG and no history of AMI. Patients who underwent perfusion imaging had a lower rate of hospital admissions (47.5% versus 56.1%, Relative Risk 0.87, p<0.001), a lower rate of unnecessary hospital admissions (42% versus 52%, p<0.001) and a higher rate of direct discharges from the emergency department (44% versus 52.6%, Relative Risk 0.84, p<0.001) without differences in 30-days outcome (death, revascularization or coronary angiogram). A normal technetium-99M sestamibi was associated with a low 30-days event rate (AMI of 0.6%), whereas an abnormal technetium-99M sestamibi was associated with higher risk of AMI (10.3%(56).

Thus, immediate perfusion imaging has high negative predictive value. According to the above mentioned study, it may improve triage decision making. However, the rate of unnecessary hospital admissions was still very high and compared to the standard protocol the 30 days adverse outcomes were similar. Therefore, it has to be questioned if immediate perfusion imaging is cost-effective compared to a standard rule out protocol.

Recently, a randomized trial showed that a strategy based on perfusion imaging results in patients with chest pain and non-diagnostic ECG was cost-saving ($1843 lower median in-hospital costs and 2 days shorter median lengths of stay) compared to a conventional strategy, i.e. treatment according to the judgement of the attending physician who was blinded to the perfusion imaging results. In this study, a negative perfusion imaging was followed by an exercise tolerance testing. Patients were discharged if the exercise testing
was negative. The 30 days event rates were similar for both groups. However, the study was small (46 patients: 23 patients in each arm) and the conventional arm was not standardized(61). Another larger study (209 patients) reported also lower costs ($453 lower median costs) if triage of patients with chest pain and a normal or non-diagnostic ECG (to admit or discharge) was based on immediate perfusion imaging results (discharge of patients with normal results) instead of triage based on clinical and ECG variables(62). A small study (50 patients) showed that the management decisions made by the physician in patients with unexplained chest pain were altered in a substantial proportion of patients after knowing the result of the perfusion imaging. The management decisions were evaluated by a questionnaire before and after the result of the perfusion imaging was known. The absolute cost saving was $786 per patient(63). Another study reported a potential mean cost savings of up to $4258 per patient if the criterion not to admit patients with a normal perfusion imaging was used (a 57% reduction in hospital admissions)(54).

The above mentioned studies show that immediate perfusion imaging may be cost-effective. However, these studies did not compare immediate perfusion imaging with a standard rule out protocol, including serial ECG, and serial marker measurement (followed by stress testing). In addition, the study populations were small and follow up was reported only in one study.

c. Comparison of resting echocardiogram and resting perfusion imaging

Studies comparing the diagnostic value of resting 2D echocardiogram and resting technetium 99M-sestamibi in chest pain patients with non-ischemic ECG showed an overall agreement between the two tests of 90% (50;53). The sensitivity of the test will be higher if the imaging is performed early after the onset of symptoms or during ongoing chest pain. The specificity of the test will be higher if the imaging is performed in patients without prior myocardial infarction. In patients with known coronary artery disease serial imaging may be required to discriminate between new and old myocardial infarction. In addition, the negative predictive value of both techniques is excellent. Thus, both echocardiography and perfusion imaging have similar diagnostic and prognostic value in patients presenting with chest pain. Therefore, either an echocardiogram or perfusion imaging may be used for rule-out purposes. However, each technique has potential advantages and limitations. It has been shown that rule-out protocols using immediate nuclear imaging at a chest pain center may be cost saving(61-63). An echocardiogram, on
the other hand, is less costly. In addition, echocardiography is a bedside technique and it may reveal either ischemic or non-ischemic causes of chest pain (e.g. pulmonary embolism, aortic dissection). Perfusion imaging may be performed in patients with poor echocardiographic image and it may provide information on ventricular function as well(64). Both for echocardiogram and perfusion imaging trained personnel is required for the performance and interpretation, thus both techniques may not be readily available.

d. Magnetic resonance imaging
With cardiac magnetic resonance imaging it is possible to evaluate regional contractile function, perfusion and viability. Therefore, it may have diagnostic value and prognostic value in the patients presenting with chest pain. So far only one report described the diagnostic value in such patients, i.e. 161 patients presenting with chest pain and an ECG not diagnostic of AMI (sensitivity and specificity for the detection of ACS were 84% and 85%, respectively)(65). There are no studies concerning the prognostic value of magnetic resonance imaging in rule-out populations.

V. Pre-discharge stress tests

a. Exercise electrocardiogram
Exercise electrocardiography (exercise ECG) is the most readily available stress test for risk stratification in patients without ongoing chest pain and with an inconclusive ECG and normal serial markers of necrosis. It has been studied in low risk chest pain patients, identified by an uneventful observation period, normal resting ECG’s and normal biochemical markers. Several studies have shown that this technique can identify low risk patients(66;67). Polanczyck et al. demonstrated that patients with a negative exercise ECG after a standard rule-out protocol including normal serial CK-MB<sub>mass</sub> results, have a very low 6 months cardiac event rate (4/195 (2%)), whereas patients with a positive or inconclusive exercise ECG were at increased risk for cardiac events (12/81 (15%), p<0.01), readmission (31% versus 12%, p<0.01) and emergency room visits (29% versus 12%). In this study, patients were included only if they underwent an exercise test. The decision to perform an exercise test was made by the attending physician. Considering this potential selection bias, the patient population may not represent a typical chest pain population presenting to the emergency department: the patients may be at either lower or higher risk, because physicians may not perform the exercise test in patients at very low
risk or in patients at very high risk, i.e. with unstable angina. This potential selection bias resulted in a high negative predictive value (98%) (table)(68). However, the decision either to perform or not to perform an exercise test may reflect daily clinical practice.

An immediate (i.e. within one hour after presentation) exercise ECG may be performed safely in selected low risk patients (on the basis of ECG (normal or only non-specific repolarization abnormalities), clinical findings, an initial marker measurement in selected patients, chest roentgenogram and the ability to exercise(69-71). One of the studies included only patients with known coronary artery disease. In this study, only 20% of the screened patients were included, with inability to exercise being the main reason for exclusion. The patients with normal exercise ECG were discharged home, having no future cardiac events (table). This was confirmed by a large study (1000 low-risk patients including 7.5% patients with previously documented CAD)(table). The 30 days event rate in patients with a negative exercise ECG was 1/640 (0.2%)(70).

Although it has been shown that immediate exercise ECG may be performed safely in selected low risk patients, there is a risk that patients with non-Q-wave myocardial infarction undergo exercise ECG (3.2% (4/125))(70). Therefore, serial marker measurements should be obtained prior to exercise testing. Thus, in selected low risk chest pain patients, identified by a standard rule out protocol including normal serial marker measurements, an exercise ECG is acceptably safe and should be used as the first-line non-invasive stress test for ambulatory patients with normal resting ECG. Patients unable to exercise or with an uninterpretable ECG at rest or during exercise or inconclusive exercise ECG findings require stress imaging(16).

b. Stress echocardiography

Only 1 prospective study comprising more than 100 patients with chest pain has been performed so far for the evaluation of the prognostic value of stress echocardiography. Dobutamine stress echocardiogram (DSE) performed after ruling out ACS by standard protocol including serial troponin T, showed to have independent prognostic value for future cardiac events. A negative DSE was associated with low risk during follow-up (1/351 (0.3%) patients with cardiac death or AMI and 13/351 (3.7%) patients with rehospitalization for unstable angina or revascularization(39)(table).

Thus, dobutamine stress echocardiography can be used as an alternative stress test to further risk stratify chest pain patients in whom ACS is ruled out by standard protocol.
c. stress perfusion imaging

Several studies used stress perfusion imaging in patients with chest pain presenting to the emergency department. In one study, 805/1775 patients, identified as having possible ACS by means of a negative 2-hour rule out protocol and physicians judgement, underwent rest and stress perfusion imaging. In these patients, nuclear stress imaging was more sensitive (97.3 versus 71.2%, p<0.0001) and specific (87.7 versus 72.6%, p<0.0001) than nuclear rest imaging for 30 days ACS(57)(table). However, another study showed that both stress perfusion imaging and rest perfusion imaging have similar accuracy and high negative predictive value if the stress imaging is performed in patients with delayed presentation (>3 hours of chest pain) and the rest imaging is performed in patients with early presentation (72) (table). In a similar but larger patient cohort, stress perfusion imaging had a sensitivity of 99.1% and a specificity of 87.4%, for 30 days ACS(73)(table). In another large study (n=1195), 509 low risk patients underwent stress perfusion imaging (the decision to perform stress perfusion imaging was left to the discretion of the medical team). The 3 months cardiac event rate was lower (1/320 (0.3%), 1 death, no AMI) in patients with a normal test than in patients with an abnormal test (6/189 (3.1%), 1 death and 5 AMI)(74).

Nuclear stress imaging as part of a rule-out protocol may be of value in selected patients.

We may conclude that the sensitivity and specificity is better for stress imaging than for exercise ECG. However, patients in whom acute coronary syndrome has been ruled out by a standard rule out protocol, including serial ECG, serial markers of myocardial damage, and an observation period, form a low risk group. In such patients performance of stress imaging may lead to high costs and a high rate of false positives. Therefore, exercise electrocardiography remains the most readily available and non-expensive tool for risk stratification in patients in whom acute coronary syndrome has been ruled out. The only exceptions are patients who are unable to perform exercise or who have an uninterpretable electrocardiogram. In such patients stress imaging is an alternative. The diagnostic accuracy of DSE and stress perfusion imaging is comparable(19). However, dobutamine stress echocardiogram has several advantages compared to stress perfusion imaging: it may be used as a bedside test, it provides information on cardiac anatomy and left ventricular function, it is more readily available, it is less time consuming and it is less costly.
VI. Pre-discharge coronary angiography

In a randomized trial comparing routine pre-discharge coronary angiography with pre-discharge exercise ECG in patients with chest pain after ruling out ACS, it has been demonstrated that the coronary angiogram was not superior to a pre-discharge exercise electrocardiogram in predicting risk (death or AMI were 0% during 1 year follow-up in both groups). However, coronary artery disease was detected more often (23/125 (19%) versus 9/123 (7%), p=0.012), which resulted in more, potentially unnecessary, revascularizations (14/123 (11%) versus 5/125 (4%))(75). It has been shown before that revascularization itself has a risk of procedure-related complications(76). For this reason, pre-discharge coronary angiography without prior ischemia detection test is not recommended in low risk chest pain patients(77).

VII. Observation period

In a selected chest pain population, an observation period of 12 to 24 hours should be sufficient to identify patients at low risk for myocardial infarction or major complications (30;31). Recently even shorter pre-discharge observation periods have been advocated(40;43;66;73;78). After an observation period of 9.2 hours, 97/212 intermediate risk (AHCPR) patients were identified as low risk (no recurrent chest pain, negative serial CK-MB and a negative stress test) and discharged. No major events occurred in these patients during six months follow-up(78) (table).

Another large study (n=13672) showed that a screening program (including a clinical chest pain scoring list, normal ECG and normal marker measurement) was able to identify 4427 low risk patients. Of these patients, 2672 had a low chest pain score and were sent home within 6 hours after a first line negative evaluation. At 6 months follow-up the event rate (AMI, UA, and coronary artery disease) was 0.2%. The other 1755 patients had a high chest pain score and were admitted to the chest pain unit for further evaluation. After a normal observation and a normal stress test, an additional 870 patients were discharged within 24 hours. No cardiac events occurred in these patients during follow-up (negative predictive value of 100%)(79).

Even a shorter observation period of 2 hours in selected patients (on the basis of the physician’s estimate of likelihood of ACS after history, physical examination, and a 2
hours evaluation protocol consisting of continuous ST segment monitoring and serial ECG’s, serial CK-MB and serial troponin T measurements followed by selective nuclear stress testing) have been proposed to exclude ACS. The 30 days adverse outcome (ACS, revascularization, life threatening cardiac complication or death) was 0.5% (7/1530)(73) (table).

Thus, the length of the observation period depends on the selection of patients presenting with chest pain and the tests used as part of the rule out protocol.

**Clinical Implication of the different diagnostic modalities**

In patients presenting with chest pain to the emergency department or chest pain unit a clinical history should be taken and a physical examination and a 12 lead ECG should be performed, preferably within 10 minutes.

Ischemic ECG changes identify patients with ACS, i.e. patients at high risk. However, a normal or non-diagnostic serial ECG does not exclude ACS. Early myocardial resting imaging may improve risk stratification, but it will have the highest diagnostic yield in patients with ongoing chest pain without a history of coronary artery disease. However, normal resting imaging does not exclude ACS either. Therefore, during the observation period, serial/continuous ECG monitoring should be performed together with serial measurement of markers of myocardial damage. Normal serial ECG’s and normal markers of myocardial damage do not exclude ACS, and thus further testing is needed. In such patients, exercise ECG should be performed because it is the most readily available and non-expensive tool compared to other stress tests. Using such a combined diagnostic approach results in discharge of patients with a residual risk of subsequent adverse cardiac events of 0.8% - 2.0%. Patients who are unable to exercise or patients with uninterpretable ECG may be tested with DSE which is more available and less costly than perfusion stress imaging.

Future studies must focus on reducing the risk even more. So far, markers of inflammation in combination with negative serial troponine seem to be promising in the early triage of patients with chest pain. However, these findings need confirmation before markers of inflammation can be used in a standard rule out protocol. Other markers, such as myeloperoxidase, may have additional value as well, but should be tested in rule out populations. Other diagnostic tools, such as magnetic resonance imaging or immediate
resting echocardiogram with handheld echo-equipment, may show additional value in the future.

**Patient with symptoms**

**Suggestive of myocardial ischemia**

- **History**
- **Clinical features**
- **Observation:**
  - ECG Serial/Continuous
  - Markers Serial
  - Imaging Left Ventricle

**HIGH RISK**

**Urgent management**

**NOT AT HIGH RISK**

**Stress test**
- Exercise ECG
- Pharmacological stress test

**LOW RISK**

**INTERMEDIATE RISK**

**Discharge**

**Further evaluation (in-hospital/out-patient clinic)**

**Figure 1.** shows a flow chart that may be used in patients presenting with chest pain.
<table>
<thead>
<tr>
<th>Method</th>
<th>Study</th>
<th>Endpoint</th>
<th>Location</th>
<th>Follow up</th>
<th>Event rate</th>
<th>T+/T-</th>
<th>N</th>
<th>Sens</th>
<th>Spec</th>
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